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Testosterone therapy for high-risk prostate cancer survivors: a systematic review and meta-analysis

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# **Testosterone therapy for high-risk prostate cancer survivors: a systematic review and meta-analysis**

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**Abstract**

A systematic review and meta-analysis was performed to determine the relationship between testosterone therapy and risk of recurrence in testosterone-deficient survivors of curatively treated high-risk prostate cancer. Primary outcome was the risk of biochemical recurrence (BCR) in 109 high-risk patients in 13 included studies (1997-2017). Biochemical and symptomatic effects of therapy were also reviewed. The BCR rate was 0.00 (0.00-0.05), lower than the expected rate for high-risk prostate cancer survivors, suggesting that testosterone therapy may not increase their BCR risk. However, this is uncertain as the available evidence is of very low quality. Testosterone therapy remains investigational in this group.

## Introduction

Testosterone deficiency is increasingly diagnosed in survivors of prostate cancer (1, 2). It can severely impact quality of life as well as physical and mental health: effects include reduced libido, osteoporosis and cognitive impairment (1, 3-5). It has also been implicated in various comorbidities, such as diabetes and obesity (6), and correlates with reduced life expectancy. Although the relationship between testosterone therapy and cardiovascular health is controversial (7), testosterone therapy has wide-ranging benefits for those suffering from deficiency (8). Despite this, testosterone-deficient patients with a history of prostate cancer, especially high-risk prostate cancer, are not routinely treated (1, 2, 9-13).

The origins of concerns and controversy about the relationship between testosterone and prostate cancer date back to a landmark study by Huggins and Hodges in 1941. (9) They found that in both healthy controls and in men with prostatic malignancy, injecting androgens increased their serum phosphatase levels, indicating increased neoplastic activity.

Conversely, both castration and oestrogenic injections reduced their serum phosphatase levels. The conclusion was that prostate cancer progression could be worsened by increasing androgen levels and slowed by castration or administration of oestrogen. A further study by Huggins and Hodges demonstrated clinical improvement in patients with advanced prostatic malignancy following castration, as well as exacerbation of symptoms with administration of exogenous testosterone. (14) This work would go on to earn Huggins the 1966 Nobel Prize in Physiology and Medicine. It was echoed by subsequent studies documenting negative outcomes of administering exogenous testosterone to patients with advanced or metastatic prostate cancer. (11, 12) Thus the androgen-dependency theory, the rationale for the use of

androgen-deprivation therapy (ADT) to treat prostate cancer, was formed: the more testosterone the greater the prostate cancer risk. (2)

Despite the enduring impact of the androgen-dependency theory on clinical practice, it is contradicted by recent findings that neither high endogenous nor exogenous testosterone levels increase the risk of *de novo* or recurrent prostate cancer (15, 16). Contrary to expectations, low testosterone levels have been found to correlate with development of more aggressive prostate cancer (2, 17), while low recurrence rates have been reported in patients receiving testosterone while they have active prostate cancer (18-22). Research has even begun into the therapeutic potential of high dose testosterone and 'bipolar androgen therapy' to treat prostate cancer (23, 24). New theories have emerged, including the prostate saturation model proposed by Morgentaler et al (6), whereby prostate cells are vulnerable to changes in testosterone level at low levels, but prostatic androgen receptors become saturated at 250 ng/ml of serum testosterone, beyond which increases in testosterone no longer affect prostate growth or neoplastic activity (1, 6, 10, 25).

To date, no systematic reviews have been published on testosterone therapy in survivors of specifically high-risk prostate cancer. Despite shifting attitudes, the March 2015 European Urological Association guidelines recommend that only patients with a history of low-risk prostate cancer be cautiously treated after attempts to treat comorbidities and improve lifestyle (5). This review aims to clarify whether survivors of curatively treated high-risk prostate cancer can be offered testosterone therapy to treat testosterone deficiency without increasing their risk of biochemical recurrence of prostate cancer. This is assessed by comparing the risk of biochemical recurrence (BCR) in testosterone-deficient survivors of

curatively treated high-risk prostate cancer receiving testosterone therapy against expected recurrence rates in survivors of curatively treated high-risk prostate cancer.

## **Materials and methods**

### **Search strategy**

This review followed PRISMA guidelines. The review was registered on PROSPERO on 18/01/2017 under the registration number CRD42017055501. A literature search was performed in MEDLINE via Pubmed, Embase via Ovid and Web of Knowledge. Reference lists were consulted and grey literature was searched via Opengrey and Opendoar. Search terms included: Androgen/Testosterone, Therapy/Treatment/Supplementation/Replacement/Exogenous, Prostate Cancer.

### **Study selection**

Of 72 relevant studies, 13 met criteria for inclusion (3, 10, 25-35). Primary human studies were included, and reviews, systematic reviews and meta-analyses were excluded. Studies were included if high-risk patients had undergone curative prostate cancer treatment: radical prostatectomy, radiotherapy, high-intensity focused ultrasound, cryotherapy or proton therapy. Studies in which high-risk patients had on-going prostate cancer at initiation of

testosterone therapy, or who had undergone only ADT or surgical castration, were excluded. Studies in which patients had undergone ADT in addition to curative therapy were included. Length of follow-up of patients is a key factor in determining the rate of BCR, as the number of recurrences in a group is expected to increase over time. However, due to limited available data on follow-up of high-risk patients, no minimum follow-up period was applied. Similarly, due to the small numbers of patients and studies available, no minimum number of high-risk patients was applied. Studies were excluded if they did not include sufficient data to stratify the patients by risk level. Abstracts were included where sufficient data was available. Authors of conference abstracts were contacted, and three abstracts were excluded due to cohort overlap with full publications. Five abstracts lacked the detailed patient characteristics necessary for risk grouping and inclusion. Figure 1 presents the PRISMA flow diagram of the literature search process. The last search date was 20/01/2017.

### **Data extraction**

The 13 included studies were reviewed to identify study design, patient characteristics, treatment methods and outcomes. Data on the length of follow-up from initiation of testosterone therapy and the methods of administration of testosterone therapy was taken for all of the studies, but was not available for the high-risk group specifically. The primary outcome was rate of BCR. Secondary outcomes were changes to deficiency symptoms, changes to testosterone level, PSA changes and adverse effects of treatment during testosterone therapy. A quality assessment was performed using the validated IHE Quality Assessment Checklist for Case Series Studies (36-38). An additional assessment of level of evidence was performed using the Oxford Centre for Evidence-Based Medicine (OCEBM)



2011 Levels of Evidence (39). There are several classifications of risk level of prostate cancer survivors. The d'Amico criteria classify patients as high-risk if before prostate cancer treatment they have a Gleason score of 8 or greater, PSA of over 20 ng/ml, or clinical stage of T2c or greater (40). Seven of the included studies explicitly grouped their patients by risk (10, 25-27, 29, 31, 41). Of these studies, three followed the d'Amico criteria, two followed the National Comprehensive Cancer Network guidelines (high risk defined as T3a or greater, Gleason 8 or greater, PSA greater than 20 mg/ml) (29, 31) and two defined high risk as having a Gleason score greater than 8, positive surgical margins or positive lymph nodes after radical prostatectomy (10, 41). For these studies, the authors' definition of high risk was accepted. Six of the included studies were not designed to group patients by risk level (3, 28, 30, 33-35), but included sufficient information to ascertain patients' risk level using the d'Amico criteria.

### **Data processing**

Due to the lack of comparative randomised control trials, a single-arm meta-analysis was performed. A standard protocol could not be used because of the inclusion of studies with zero incidence of BCR in the data set. To include these low event rates, meta-analysis was performed using the Metaprop tool in Stata/MP 14.2. A random effects model with exact confidence intervals was used. A Freeman-Tukey double arcsine transformation was used to allow inclusion of studies with zero cases of BCR (42, 43). Heterogeneity was measured in Metaprop using Cochran's Q test and the  $I^2$  index. A funnel plot to assess publication bias was created using the Metafunnel tool in Stata/MP 14.2. The Stata/MP 14.2 is a program of Stata Corp LLC.

## Results

### Primary outcome

The 13 studies identified for inclusion are described in Table 1. The studies included a total of 608 patients, of which 109 had a history of high-risk prostate cancer. There was variation in the method of administration of testosterone therapy and in the length of follow-up from its initiation, ranging from one to 189.3 months. Figure 2A demonstrates the primary outcome of this review as a forest plot: at 0.00 (confidence interval 0.00-0.05), there was no significant overall BCR rate in survivors of curatively treated high-risk prostate cancer. Thus the meta-analysis indicates that testosterone therapy did not cause increased rates of recurrence in this group. The very low  $I^2$ -value suggests that 0.00% of the variation in the included studies may have been due to statistical heterogeneity and the p-value of 0.72 indicates that the statistical heterogeneity in the included studies may not be significant, supporting the reliability of the review (Figure 2A). However, these statistical tests of heterogeneity may have been underpowered because of the small number of included studies and their small sample sizes (44). The funnel plot (Figure 2B) does not reveal any asymmetry, which would indicate publication bias. No further subgroup analysis could be performed due to small study sizes.

### Secondary outcomes

Overall, the included studies found small increases in PSA, increases in testosterone, improvements to patients' symptoms of testosterone deficiency and few undesired side effects of testosterone therapy. However, these were inconsistently measured in the included studies. Additionally, the secondary outcomes were not grouped by patients' risk level in the included studies, so unlike the primary outcome cannot be evaluated for high-risk survivors specifically. Nine studies identified increases and transient rises in PSA that did not meet authors' recurrence criteria. All of the 10 studies that documented testosterone levels found them to be significantly increased, with the exception of a non-significant increase in Pastuszak et al's high-risk patients (10). Symptom changes were monitored in eight studies. Two studies reported using the EPIC (Expanded Prostate Cancer Index Composite) questionnaire (29, 35), whilst others relied on subjective questioning or other methods. Patients in two of those eight studies were treated concurrently with phosphodiesterase-5 inhibitors or intracavernosal triple therapy injections for erectile dysfunction, and patients in six of the included studies had received ADT as part of their prostate cancer management, which may have affected symptom improvements. That being said, all eight studies reported either a mean improvement in symptoms or an improvement in most patients. Only nine patients reported a lack of symptom improvement, five of whom discontinued therapy after a short follow-up of one to three months from its initiation – possibly too soon to reap the benefits of therapy. Out of 608 patients, of whom 109 were high-risk, there were only two cases of discontinuation of therapy due to other adverse effects (headaches and excessive testosterone). Two studies reported small increases in haemoglobin, but no cases of erythrocytosis (a known side effect of testosterone therapy) requiring treatment (5).

### **Strengths of the review**

To our knowledge, this review is the first meta-analysis to shed light on the benefits and risks of prescribing testosterone therapy to this specific population of high-risk survivors of prostate cancer. Risk stratification of patients is important as testosterone therapy becomes increasingly studied and prescribed because prostate cancer risk level is used to inform clinical guidelines and treatment decisions. This review demonstrates for the first time that the current evidence available, although of very low quality, is in favour of treating these patients.

## **Comment**

### **Primary outcome and previous literature**

The meta-analysis identified a negligible rate of recurrence of 0.00 (0.00-0.05). In the absence of randomised controlled trials, this rate of recurrence can only be compared to published BCR rates of high-risk prostate cancer in men without testosterone deficiency or treatment. This, like the reference group in Pastuszak et al's study, the only comparative study included in this review (10), does not account for a possible difference in outcome between survivors of prostate cancer with normal testosterone levels and survivors suffering with untreated testosterone deficiency. The literature values for BCR rates in high-risk prostate cancer survivors vary. Kim et al found a 16% and 48% risk of BCR at 27 and 28 months after radical prostatectomy and radiotherapy respectively (45), while Arcangeli et al

found BCR rates of 13.2% for radiation therapy and 30.2% for prostatectomy-treated patients at three years (46). At five years, d'Amico et al. suggest a 50% risk of BCR after radical prostatectomy for high-risk patients (40). Thus the recurrence rate in this review is significantly lower than expected rates for patients of equivalent risk. This might indicate that testosterone therapy could be prescribed in this group of patients without increased risk of recurrence of disease compared to a population of high-risk prostate cancer survivors. This is in agreement with Pastuszak et al's finding that their reference group of high-risk non-hypogonadal men had a higher recurrence rate than their high-risk testosterone treatment group (10).

### **Secondary outcomes and previous literature**

The secondary outcomes of the review, although they could not be assessed for high-risk patients specifically due to limited data in the included studies, are in line with previous literature. In this review, testosterone therapy produced many cases of benign PSA increase. In literature, studies have consistently found small increases in PSA in some patients commencing therapy, but either no cases of BCR or a recurrence rate lower than that expected without therapy (47). The promising secondary results of this review also suggest that testosterone therapy was effective in improving symptoms of deficiency in most patients and that it caused very few non-recurrence adverse effects. This is in agreement with published evidence for testosterone therapy in men with testosterone deficiency: a meta-analysis by Zheng et al established that therapy improves symptoms, increases testosterone levels and does not cause serious adverse reactions (8, 48).

## Limitations of the review

The BCR rate in this review was unexpectedly low compared to BCR rates in high-risk patients in literature. Rather than pointing towards a protective effect of testosterone therapy, this is likely to be the result of limitations of the review. Several potential sources of bias may have led to the underestimation of risks of treatment. Notably, the average follow-up time from the initiation of testosterone therapy was 30.5 months and varied greatly, with some patients being followed for as little as one month. This is not long enough to determine the safety of long-term testosterone therapy, given that high-risk patients have been found to experience a peak in BCR at four to six years (49). Additionally, although Figure 2B does not reveal any publication bias, five abstracts were excluded from the review because they lacked the detailed patient characteristics necessary for risk grouping. Furthermore, patient selection was neither randomised nor consecutive and was vulnerable to selection bias: it is likely that patients perceived to be lower risk, even within the high-risk category, were chosen for treatment with this controversial therapy. There may also have been reporting bias whereby authors were more likely to retrospectively include patients who were successfully treated, or attrition bias if treatment was discontinued quickly in patients showing signs of adverse effects or recurrence.

Other limitations included the small number of patients and studies, which demonstrates the limited research into testosterone therapy for this high-risk group, and the quality of evidence of those studies. 11 of 13 included studies were observational, non-randomised, non-blinded

and non-controlled case series or studies. Pastuszak et al (10) did compare their patients to a group not receiving testosterone therapy but the reference patients were not testosterone deficient and not an ideal control group. Due to the lack of a control group and the low event rate, an unconventional single-arm meta-analysis was performed. 10 retrospective studies that often provided incomplete information were included in the review. The prospective studies, in turn, may have been vulnerable to information bias in the recording of data. (3, 30, 34) 10 studies were single centre and 11 were North American, limiting their generalisability. All of the studies had an OCEBM Level of Evidence of just four out of five, demonstrating their very low quality of evidence. IHE Quality Assessment, similarly, revealed an average level of evidence of just 8.6 out of 18. The average score of 10 for the four studies that identified cases of BCR compared to an average of 7.7 for those that did not, suggesting that adverse events might have been missed by less robust methodology. The IHE scores may have been biased against the three included studies for which only conference abstracts were available, as they had less available details of patients and methodology – nevertheless, the very low level of evidence overall leaves us in need of larger scale prospective trials to obtain more reliable data. Furthermore, six studies were not designed to look specifically at high-risk patients and the included studies were statistically underpowered to individually assess the effect of testosterone therapy on high-risk patients.

There was significant variation in methods and definitions between studies. In addition to variation in follow-up period, testosterone therapy varied by route of administration: the various methods used were oral administration, subcutaneous pellets, intramuscular injections, and transdermal gels and patches. There were also differences in definition of testosterone deficiency and indications for prescribing testosterone therapy, reflecting inconsistency in the literature and adding to the clinical heterogeneity of the review. All

patients experienced symptoms of testosterone deficiency prior to starting therapy, with the exception of three men treated by Kühn et al with low serum testosterone but no symptoms (28). Conversely, Pastuszak et al treated men with symptoms of deficiency even if their testosterone levels were in normal range (10, 28). Only six studies included specific threshold serum testosterone levels below which therapy was initiated, ranging from serum testosterone of 300 to 350 ng/dl and free serum testosterone of 10.0 to 11.7 ng/dl. Testosterone therapy was prescribed after different time periods from the end of prostate cancer treatment: in theory, symptom improvements and PSA changes attributed to early testosterone therapy could have been due to the prolonged effects of prostate cancer treatment. Additionally, there was inconsistency in the definition of high-risk prostate cancer. The high-risk patients in nine of the included studies matched the d'Amico criteria, but two studies used the National Comprehensive Cancer Network guidelines (29, 31) and two studies defined high risk as having a Gleason score greater than 8, positive surgical margins or positive lymph nodes after radical prostatectomy (10, 41). The patients also received a range of treatments for prostate cancer. Notably, patients in six of the included studies were treated with ADT, which can lead to extended reductions in testosterone level, especially after use for over 36 months (50), and may have contributed to the patients' testosterone deficiency and reaction to testosterone therapy.

A final limitation was the use of BCR as the primary outcome measure. The BCR rates varied widely from zero to 50%, largely due to the small numbers of high-risk patients in individual studies. There was inconsistency in the definition of BCR, which is an already unreliable measure of recurrence. In some cases recurrence may not cause BCR, whilst in others BCR can be a 'false alarm,' especially given that small transient or sustained PSA rises can occur with initiation of testosterone therapy, in line with the prostate saturation model. (26) Such



risks in PSA were documented in nine of the included studies, and small PSA rises have even been found in placebo groups in studies of testosterone therapy in hypogonadal men. (25) Indeed, the presence of BCR did not indicate the patients' outcome at last follow-up in the included studies. Of the nine cases of BCR, five were in radiotherapy patients and four were in prostatectomy patients, with large variation in their outcomes. Two were found to be disease-free on further histological or radiological investigation, whereas five began salvage therapy, including one who developed pelvic metastases. Two had unclear outcomes: one discontinued therapy but their PSA remained elevated, and the other was not investigated further for evidence of disease but their PSA continued to rise, reaching 40 ng/ml at last follow-up (10). This suggests that the rate of histological or radiological recurrence in these studies was even lower than the rate of BCR, and further demonstrates the unreliability of BCR as a measure of recurrence.

### **Recommendations for clinical practice**

The results of this review suggest that there might not be any increased risk of BCR with testosterone therapy in testosterone-deficient survivors of curatively treated high-risk prostate cancer. The secondary outcomes point towards testosterone therapy improving symptoms of testosterone deficiency and quality of life in this population of patients. Nevertheless, the available evidence is of very low quality and should be applied to clinical practice with caution. Decisions to start and continue therapy must be made with detailed discussion of potential benefits and risks with patients, including discussing the current lack of robust evidence and discussing possible adverse effects and cardiovascular risk. It should be offered to patients who suffer from symptoms of deficiency that severely impact their quality of life

and cannot be attributed to comorbidities. Starting treatment with short-acting formulations is recommended, as it allows for rapid withdrawal in case of adverse effects or suspected recurrence (5). We echo recommendations (3, 34) to wait for PSA to reach a nadir, ideally below 1 ng/ml, between prostate cancer treatment and initiation of testosterone therapy to reduce confusion between benign post-treatment PSA increases and BCR. Crucially, patients should be fully screened for active disease before initiating therapy, and monitored closely during treatment.

### **Recommendations for future research**

We would recommend that future research into treatment of survivors of prostate cancer with testosterone therapy group patients by risk for all study outcomes. We recommend that trials be prospective and include a control group of prostate cancer survivors with symptoms of testosterone deficiency but not receiving testosterone therapy. Randomised controlled trials would significantly improve the quality of the evidence. Larger trials with longer follow-up are also necessary, given the very low event rate in the included studies. Long-term follow-up over at least five years would be beneficial to establish the long-term safety of testosterone therapy, and applying a minimum length of follow-up is crucial to interpreting BCR rates. There should be clarity and consistency in the definitions of testosterone deficiency, administration of testosterone therapy and BCR. The outcomes of suspected cases of BCR should be recorded to determine both the number of cases of BCR and the number of confirmed recurrences of disease. The management of patients' prostate cancer, including the duration of ADT, should be recorded.

## Conclusions

This systematic review and meta-analysis found that there was no increased rate of BCR in survivors of curatively treated high-risk prostate cancer receiving testosterone therapy for testosterone deficiency compared to the rate of BCR in high-risk prostate cancer survivors in literature. This suggests that testosterone therapy may not present an increased recurrence risk in this group, and may be considered for patients with symptoms of testosterone deficiency. However, the body of evidence is small and of very low quality, and this therapy remains investigational in this group.

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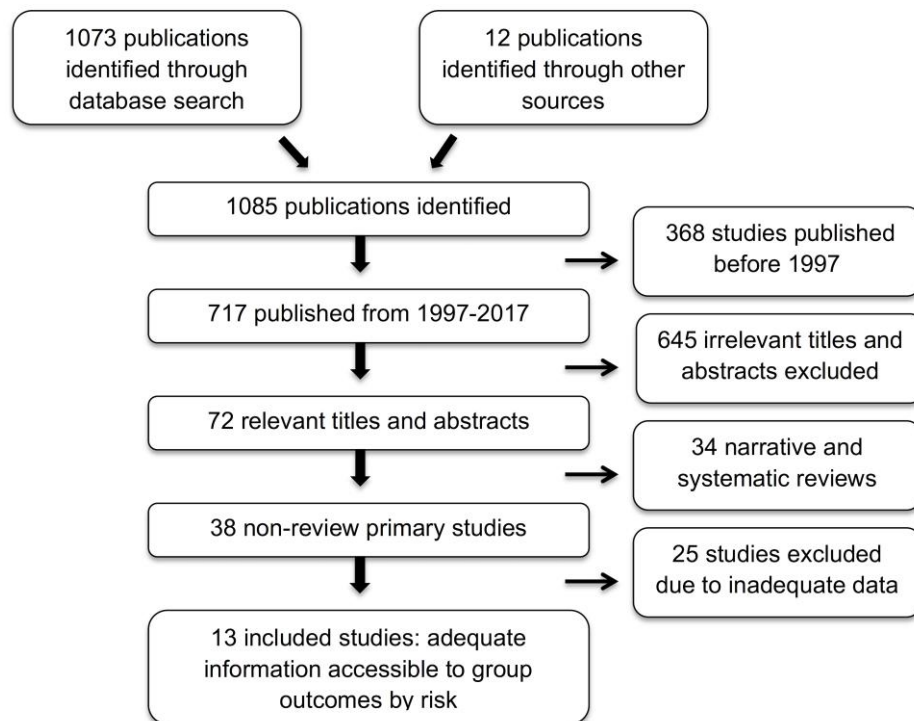
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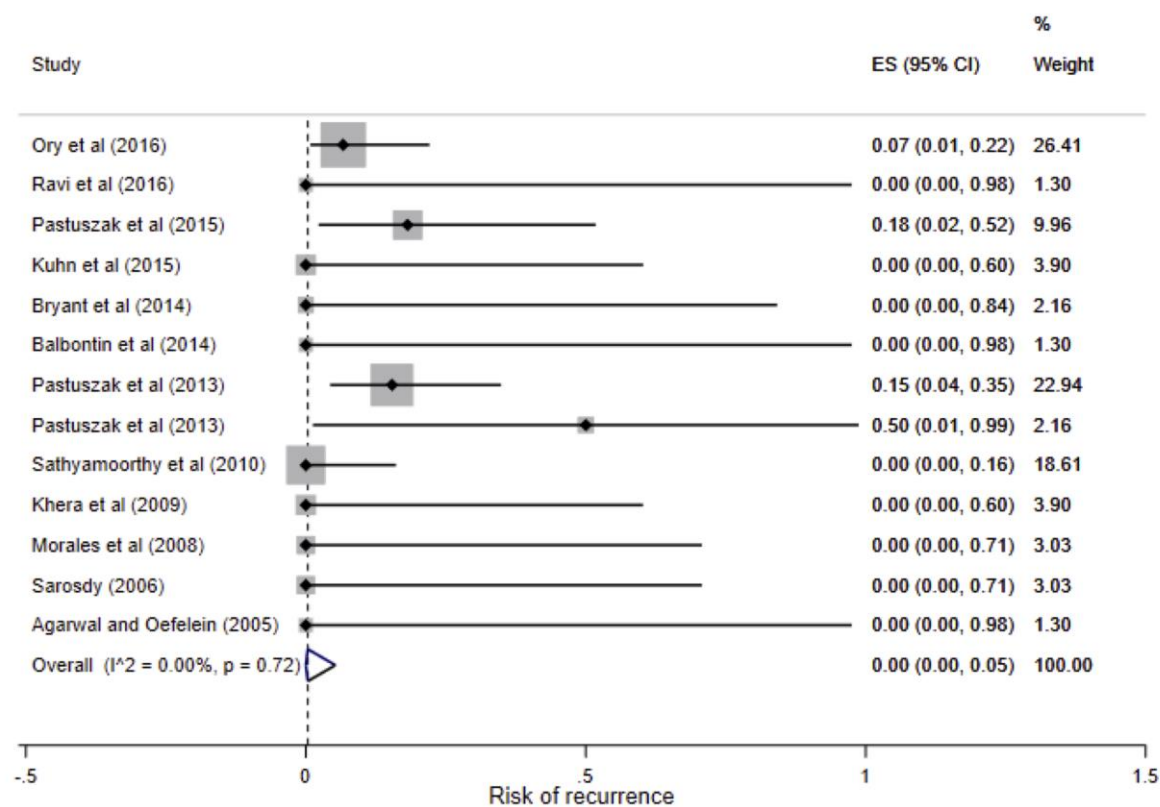
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## Figure legends

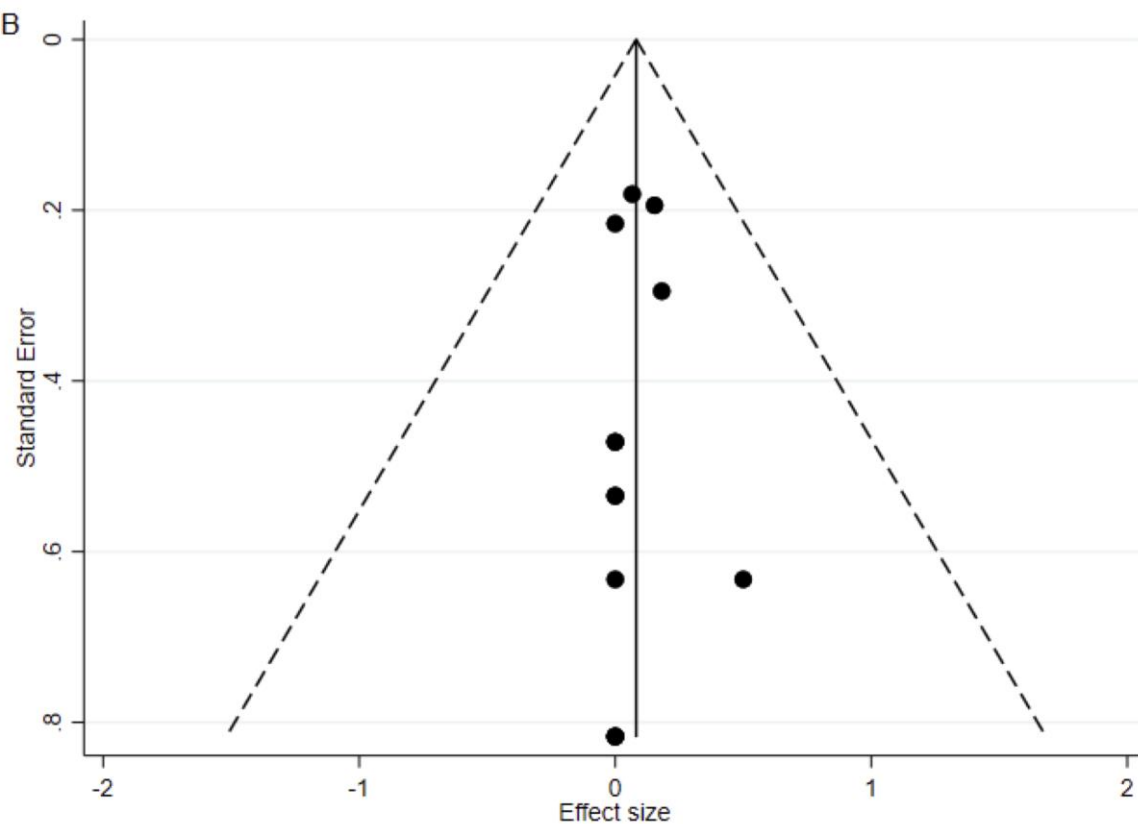


**Figure 1.** PRISMA flow chart demonstrating the literature search process.

A



B



**Figure 2.** Meta-analysis results. **A)** Forest plot demonstrating the rates of BCR in survivors of curatively treated high-risk prostate cancer in the included studies. The net risk of biochemical recurrence was 0.00 (confidence interval 0.00-0.005). The  $I^2$ -value suggests that 0.00% of the variation in the included studies may have been due to statistical heterogeneity. The p-value of 0.72 indicates that the statistical heterogeneity in the included studies may not be significant. **B)** Funnel plot of included studies does not reveal any publication bias.

**Table 1.** Characteristics of the included studies and their BCR rates in high-risk patients. BCR = Biochemical recurrence, RP = radical prostatectomy, ADT = androgen deprivation therapy, EBRT = External beam radiation therapy, HIFU = high intensity focused ultrasound.

Study	Study size (Number of high-risk patients)	IHE Score (0-18)	OCEBM Level of Evidence (1-5)	Mean / median months follow-up* period (range)	Prostate cancer treatment received (number of patients)	BCR cases (High-risk BCR cases)	% BCR in high-risk group
Ory et al. Oct 2016	82 (30)	10	4	41 (22-57)	RP +/- ADT (22)	0	0 %
					Radio-therapy +/- ADT (50)	3 (2)	9.52%
					Other +/- ADT (10)	0	0 %
Ravi et al. Apr 2016	1 (1)	6	4	-	EBRT (1)	0	0%
Pastuszak et al. Nov 2015	98 (11)	11	4	40.8 (1.5 - 147)	Radio-therapy +/- ADT (96)	6 (2)	18.2%
Kühn et al. Sept 2015	32 (4)	7	4	39.8 (12-108)	RP (26), EBRT (1),	0	0%

					brachytherapy (3), HIFU (2)		
Bryant et al. Dec 2014	23 (2)	8	4	38	Proton therapy +/- ADT	0	0%
Balbontin et al. Jul 2014	20 (1)	12	4	31 (12-48)	Brachytherapy +/- EBRT (20)	0	0%
Pastuszak et al. Aug 2013	103 (26)	9	4	27.5 (6.2-189.3)	RP +/- ADT, radiation therapy, gene therapy, chemotherapy (103)	4 (4)	15.4%
Pastuszak et al. Jan 2013	13 (2)	10	4	29.7 (2.3-67.3)	Brachytherapy (3), EBRT (10), +/- ADT (4)	1 (1)	50%
Sathyamoorthy et al. Apr 2010	133 (21)	7	4	12	RP	0	0%
Khera et al. Apr 2009	57 (4)	9	4	13 (1-99)	RP	0	0%
Morales et al. Jan 2009	5 (3)	8	4	14.5 (6-27)	EBRT	0	0%
Sarosdy. Feb 2007	31 (3)	7	4	60 (18 - 108)	Brachytherapy +/- EBRT, ADT (31)	0	0%
Agarwal and Oefelein. Feb 2005	10 (1)	8	4	19	RP (10)	0	0%

\* Follow-up period from the initiation of testosterone therapy